PATENT
Attorney Docket No.: 018512-001420US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Timothy J. Jegla

Application No.: 10/738,455

Filed: December 16, 2003

For: KV6.2, A VOLTAGE-GATED POTASSIUM CHANNEL SUBUNIT

Customer No.: 20350

Confirmation No. 9589

Examiner: SEHARASEYON, Jegatheesan

Technology Center/Art Unit: 1647

DECLARATION UNDER 37 C.F.R. §1.132 OF DR. DOUGLAS KRAFTE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Douglas Krafte, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I received my Ph.D. in Physiology from the University of Rochester. Currently I am the Vice President – Biology at Icagen, Inc. I have been at this position and related positions for 19 years. A copy of my curriculum vitae is attached hereto as **Exhibit A**.

3. The invention of the above-referenced patent application provides for the first time the polynucleotide sequence and amino acid sequence of a subunit of human Kv6.2, a member of the Kv family of voltage-gated potassium channels, and demonstrates the functional assembly of a heterologous potassium channel by this subunit and another Kv potassium channel subunit. Kv6.2 is found expressed in the brain, a part of the central nervous system (CNS).

4. I have read and am familiar with the contents of this patent application. In addition, I have read the Office Action of June 12 2007, received in this application. It is my understanding that the Examiner does not believe that the present invention is supported by a specific, substantial, and credible asserted utility or a well established utility as required by the United States Patent Laws.

5. This declaration is provided to explain that the identification of the coding sequence for Kv6.2, coupled with the demonstration of its functional expression, has a specific and substantial utility, which is credible to one of ordinary skill in the art, particularly for the purpose of drug discovery.

6. Several subfamilies of the Kv potassium channel family have previously been identified. These potassium channels are indicated in signal transduction during various biological processes such as neuronal integration, cardiac pacemaking, muscle contraction, hormone secretion, cell volume regulation, lymphocyte differentiation, and cell proliferation. Given this knowledge and the specific expression of Kv6.2 in the CNS, one of ordinary skill in the art would recognize the Kv6.2 channel as a therapeutic target for treating CNS disorders such as migraines, hearing and vision problems, psychotic disorders, and seizures. The identification of human Kv6.2 coding sequence makes it possible to screen for activators and inhibitors of Kv6.2 potassium channels. The ability to functionally express the channels is very important in a modern drug discovery environment and allows pharmaceutical researchers to identify

compounds that directly affect the channel activity. These same compounds can then be tested in other comparable functional assays to assess selectivity and determine off-target activity and the potential for side-effects. Because such activators or inhibitors can be used for treating conditions such as those named above, the present invention has a specific and real-world use. KCNQ2 is an example of a potassium channel as a target for therapeutic purposes. Loss of function mutations of KCNQ2 have been shown to cause a form of epilepsy (Singh *et al.*, 1998 *Nat. Genetics* **18**: 25-29, attached as **Exhibit B**) and the KCNQ2 channels have been targets for drug discovery programs for a number of years (see, *e.g.*, Wickenden *et al.*, 2004 *Expert Opin. Ther. Patents* **14**(4): 1-13, attached as **Exhibit C**).

7. It is well known in the art that once an ion channel has been identified, modulators of this ion channel can be routinely identified based on the coding sequence of the ion channel, functional expression, and a method for activation of the channel. The present application provides nucleic acid and amino acid sequences of human Kv6.2 as well as methods for detecting the activity of a Kv6.2 potassium channel, one of ordinary skill in the art can thus conduct routine testing to identify activators or inhibitors of a Kv6.2 potassium channel useful for modulating signal transduction in the cells where this potassium channel is present (*e.g.*, the brain), and therefore useful for treating CNS disorders such as migraines, hearing and vision problems, psychotic disorders, and seizures.

8. There are known instances where modulation of an ion channel is useful for treating a specific disease even though the channel itself may not cause the disease. For example, hypertension can be caused by a variety of illnesses such as renal disease and diabetes. Among the treatment strategies for hypertension is the use of drugs such as calcium channel blockers to relax the vasculature. Relaxing the vasculature to reduce blood pressure by blocking a calcium channel is useful and effective, even if the original cause of the hypertension is unrelated to the calcium channel itself. Similarly, it is perfectly reasonable to expect that the targeting of a Kv6.2 channel, a voltage-gated potassium channel expressed in the brain, is an appropriate strategy for treating CNS disorders, whether or not such conditions are directly

caused by altered Kv6.2 activity. Thus, the disclosure of the present application is sufficient to establish the utility of Kv6.2.

9. In the Office Actions of June 12, 2007, the Examiner apparently takes the position that the sequence information of Kv6.2 alone is insufficient to establish utility. It is respectively submitted, however, that this patent application provides not only the sequence information, but also functional expression and tissue distribution for the Kv6.2 potassium channel. In my experience, this disclosure provides the vital information necessary for a modern drug discovery effort where one expresses an ion channel of interest and subsequently identifies small molecule modulators of the ion channel in functional assays; the modulators can then be used for treating diseases and conditions relevant to the ion channel. Many of the drug discovery programs I have been associated with over the years have relied on a similar level of information and data.

10. In summary, it is my scientific opinion that one of skill in the art, at the time the application was filed, would recognize the specific and real-world utility of the Kv6.2 encoding nucleic acids of the present invention.

Date: December 7, 2007 By: _____
Douglas Krafte, Ph.D.

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Attachment (Exhibits A-C)
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